

Interstitial Lung Disease

Part I. A Multidisciplinary Approach to the Diagnosis and Assessment of Disease Activity

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SUMMARY

The value of alveolar lavage as an investigative technique was determined in patients with interstitial lung disease. Alveolar cytology was related to defined histopathological degrees of disease activity found in transbronchial biopsy specimens. The degree of disease activity as assessed by these two techniques was compared with radiological evaluation. Adequate specimens of lung tissue for histopathological evaluation were obtained by transbronchial biopsy in 95% of the subjects during the first procedure and diagnostic histopathological changes were found in 60% of the patients. In the evaluation of disease activity, the lymphocyte-macrophage (L-M) ratio and, to a lesser extent, the total alveolar cell counts correlated well with graded histopathological changes of activity. A graded radiological evaluation of activity was accurate in 14 out of 17 patients, but in 3, extreme cellular disease was not recognized. Alveolar cytological examination can be employed as a supplement to the biopsy technique for increased accuracy in the initial and follow-up evaluation of active interstitial lung disease. An approach combining transbronchial biopsy, alveolar lavage and radiography, provides a safe and accurate alternative to open lung biopsy in most patients for determining the aetiology and degree of activity of interstitial lung disease.

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The determination of aetiology and the assessment of disease activity are two major problems in patients with diffuse interstitial lung disease. These are important factors in determining the prognosis and predicting the possible benefit of vigorous treatment, for example with prolonged high doses of corticosteroids. Invasive procedures which include open lung biopsy, high speed trephine biopsy, percutaneous cutting needle biopsy, and transbronchial fibre-optic techniques have all been employed to determine the aetiology and degree of disease

activity in patients with interstitial lung disease.¹⁻⁵ The morbidity associated with these procedures make them unacceptable for repeated use in assessing disease activity in patients receiving treatment.

There have been reports on differential alveolar cell counts in patients in whom interstitial disease was diagnosed histopathologically by open lung biopsy.^{6,7} The importance of considering the cellularity of the disease process was stressed by Carrington *et al.*,¹ who found that patients with active or cellular types of interstitial disease responded well to steroid treatment.

The aim of this study was to determine the value of alveolar cytology in the initial and possible follow-up assessment of disease activity. Radiology has for many years been the standard investigative method for determining the presence and extent of involvement of interstitial lung disease. Gross changes may, however, be present without any radiological indication of the cause of the lung involvement. The accuracy of radiological estimation of disease activity was determined by a simultaneous comparison with measurements of cellular and histopathological activity. Disease activity was assessed radiologically and was correlated with a quantitative and qualitative analysis of alveolar cells and a graded histopathological estimation of disease activity. Alveolar lavage was found to be a safe and reproducible technique; the cellular analysis not only correlated well with, but also supplemented the conventional methods of determining disease activity.

SUBJECTS AND METHODS

Twenty patients with clinical and/or radiological signs of interstitial lung disease were evaluated. The following possible clinical diagnoses were entertained: sarcoidosis, interstitial disease of unknown aetiology (IDUE), pigeon-fancier's disease, and eosinophilic pneumonia. The ages of the patients ranged from 15 to 64 years and there were 13 females and 7 males in the group. Seven patients were smokers, 12 had never smoked and 1 had stopped smoking 3 months before being studied. Eighteen of the 20 patients had not received any specific treatment when they joined the study. One patient was being treated with methylprednisolone 64 mg and cyclophosphamide 100 mg daily. Another patient was on prednisone 10 mg daily for unproven sarcoidosis. The most prevalent signs and symptoms were (numbers of patients in brackets): dyspnoea (16), cough (14), weight loss (12), chest pain (10), crepitations (16), and erythema nodosum (3). Clubbing of the fingers was absent in all patients.

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Elevated erythrocyte sedimentation rates ranging between 30 mm and 135 mm/h were recorded in 11 subjects. In 17 subjects protein electrophoresis showed elevated gammaglobulin values. Arthus skin reactions and precipitin tests conducted with pigeon serum antigen were positive in 2 patients with possible pigeon-fancier's disease. Elevated serum calcium levels were present in only 2 patients, both with histopathologically proven sarcoidosis. Eosinophil counts in peripheral blood were normal in 2 patients with clinical and radiological diagnoses of chronic eosinophilic pneumonia.

Lung Function Tests

A restrictive lung function pattern as evidenced by a decrease in vital capacity (less than 74% predicted) and a flow volume curve with a restrictive pattern were present in 17 subjects. Increased elastic recoil was present in 7 of the 15 subjects in whom this was measured. A decreased CO transfer factor (single breath method) of 49-78% of the predicted normal value was recorded in 5 of the 9 patients in this group on whom this measurement was possible.

Alveolar Lavage and Transbronchial Biopsy

The vocal cords and bronchial tree were sprayed with a local anaesthetic agent and bronchoscopy was conducted after intravenous administration of droperidol 5 mg, fentanyl 0.1 mg and diazepam 20-30 mg. Under fluoroscopic control a No. 8 Courmand catheter was positioned through the bronchoscope in the right middle lobe. Cellular contamination from the mouth and larger airways was avoided by employing this technique of catheter placement. The alveolar lavage was conducted by alternating injection and suction of 10 ml aliquots of normal saline ten times at 37°C. In 5 of the patients alveolar lavage was performed on the lingula of the left upper lobe as well as on the right middle lobe, and cell counts of the right and left lungs were compared. Total and differential alveolar cell counts were also determined in 5 smokers and 5 non-smokers with clinically and radiologically normal lungs who were being investigated by bronchoscopy to exclude possible late complications of tracheostomy. Informed consent for the alveolar lavage was obtained from each individual. In patients with interstitial disease, a flexible biopsy forceps with a 3 mm cup was wedged in the periphery of the lung under fluoroscopic control and lung tissue was obtained by the transbronchial technique. In 12 patients this procedure was conducted at more than one site in the right and left lungs or in one lung, e.g. right middle and lower lobes. At least one adequate specimen was obtained from each of the remaining 8 patients. The lung perimeter was closely inspected by fluoroscopy for a possible pneumothorax before proceeding to subsequent biopsies. This was followed by chest radiograph 1-2 hours after the procedure to exclude late development of a pneumothorax. When pulmonary hypertension was suspected on clinical, radiological or electrocardiographic grounds, pulmonary artery pressures were determined at rest and

during exercise by Swan-Ganz catheterization before transbronchial biopsy. Because of the possible danger of severe haemorrhage the transbronchial technique was not employed in patients with resting pulmonary hypertension.

Total and Differential Alveolar Cell Counts

Excess mucus was removed by passing the lavage solution through cheesecloth. Cell analyses were conducted on the unfiltered solution as well as on the filtrate and no differences in the total or differential counts were found. The volume of alveolar lavage solution retrieved varied from 17 to 85 ml (mean 44 ml). Total alveolar cell counts were expressed per millilitre and not as a function of the whole retrieved volume, to prevent this variable factor from influencing the results. A Spencer Bright-Line haemocytometer was used to determine the total number of cells per millilitre of retrieved solution. With a calibrated eye-piece micrometer a differential cell count, which included macrophages, lymphocytes, neutrophils and eosinophils, was conducted on an uncentrifuged specimen by preparing slides with Leishman's and May-Grünwald-Giemsa stains.

Evidence was obtained during preliminary experiments that the cytocentrifuge technique induced loss of cells by fragmentation and possible changes in the adhesive qualities during slide preparation. Slides were therefore prepared by placing a drop of lavage fluid on a standard glass slide and by filtering off the saline solution after 2-3 minutes. This was done by gently applying a No. 1 Whatman filter paper to the meniscus of the drop. Loss of cells, even red cells, on the filter paper was negligible. Mononuclear cells were subjectively evaluated where indicated as small macrophages or large lymphocytes on the nucleus-cytoplasm ratio. In the majority of patients, differentiation between these two cell types was not problematic. The presence of abnormal cells, e.g. cancer cells, was also noted.

Histopathology

Haematoxylin and eosin and connective tissue staining was performed on all biopsy specimens. One member of the group, an experienced histopathologist, evaluated the cause and degree of histopathological activity in the lung tissue of each patient. Disease activity was estimated on a 0-4-point scale. This arbitrary assessment was based on a global impression of the population density and nature of the reacting cells in the pulmonary interstitium and alveoli. Histopathological activity included not only the presence of acute or chronic inflammatory cells, but also the presence of granulomas or active fibroblastic proliferation. All the biopsy specimens were more or less of the same size so that an approximation could be made of the percentage surface area of each tissue section in which these cellular changes were present. On the activity scale, zero indicated the absence of any signs of active disease. Low-grade activity was denoted by grade 1 (up to 10% of the area sectioned) and grade 2 (up to 25% of the area sectioned). Grades 3 and 4 (high-grade activity) represented up to 50% and 75% plus of the area sec-

tioned respectively. The arbitrary grade of activity so obtained was correlated with the total and differential alveolar cell counts obtained by alveolar lavage. The extent of permanent lung damage in the form of destruction of lung architecture by the formation of fibrous and reticulin tissue was noted.

The estimation of histopathological disease activity was controlled by regrading the biopsy specimens of 10 randomly selected patients, without the pathologist knowing from which patient's lung or lobe specific specimens were obtained. This was done 4 months after the initial assessment (Table I).

TABLE I. ESTIMATED DISEASE ACTIVITY IN THE RIGHT AND LEFT LUNGS OR IN DIFFERENT LOBES OF THE SAME LUNG

Patient	Right middle lobe	Right lower lobe	Left lower lobe
1	4 (4)	4 (4)	4 (4)
2	3 (4)	4 (4)	4 (4)
3	3 (3)	3 (2)	1 (1)
4	1 (1)	1 (1)	1 (2)
5	4 (4)	4 (4)	
6	3 (4)	3 (3)	
7		3 (4)	1 (1)
8		1 (1)	1 (1)
9	3 (4)		3 (4)
10	3 (4)		4 (3)

Grades of activity: 0 (normal lung) to 4+ (maximal activity). Revised activity values in brackets.

Radiological Evaluation

Postero-anterior and lateral chest radiographs of 17 patients were evaluated for disease activity by an experienced radiologist. The evaluation was based on the estimated intensity of lesions and on the extent of involvement of lung fields. It was assumed that a predominantly alveolar pattern would be associated with a high degree of disease activity, while a predominantly interstitial pattern or coarse fibrosis would indicate a low degree of disease activity. The presence or absence of hilar and/or mediastinal lymph node enlargement was not taken into account in assessing the activity of the pulmonary lesion. Using the following criteria and patterns, the intensity of activity was graded from 1+ to 4+, as follows: 4+ — poorly defined, blotchy, fluffy, soft, coalescent opacities; 3+ — ground-glass pattern; fine miliary pattern; small, soft, poorly defined opacities or nodules; 2+ — ill-defined, fluffy or fine reticular, nodular or reticulonodular shadowing; 1+ — questionable or minimal veiling, coarse or sharply defined reticular or reticulonodular pattern; fibrotic streaks with minimal soft shadowing; 0 — normal chest or dense fibrotic changes without any accompanying soft shadowing.

The extent of involvement was graded from 1+ to 3+ as follows: 3+ — very extensive, widespread involvement of both lungs; 2+ — moderately extensive involvement of one or both lungs; 1+ — questionable or minimal involvement of one or both lungs; 0 — normal lungs.

A total score of disease activity ranging from 0 (no activity) to 7 (maximal activity) was determined for each subject. Participants in the study conducted their evaluation independently without any knowledge of each other's results or of the clinical diagnosis.

RESULTS

Histopathology

Adequate tissue was obtained for histopathological diagnosis by the transbronchial technique during the first procedure in 19 patients (95%). All the biopsy specimens were adequate for histopathological analysis in the 12 subjects on whom multiple biopsies were performed. In 1 subject from whom no adequate specimen was obtained, a histopathological diagnosis was possible after a second transbronchial biopsy. Patients with interstitial disease were subdivided histopathologically into four subgroups. In 9 patients sarcoidosis alone was diagnosed. One patient had sarcoidosis with silicosis. Two patients had pigeon-fancier's disease. A diagnosis of IDUE was made in 6 patients. In two subjects organizing pneumonia was reported, but clinical, radiological and therapeutic evidence was found to establish the diagnosis of chronic eosinophilic pneumonia. This diagnosis will be referred to in subsequent results and in the discussion.

Disease activity was graded low (1-2+) in 6 and high (3-4+) in 14 of the 20 patients. Results of the initial and revised assessments of disease activity in different lobes are shown in Table I and indicate that in 8 of 10 patients within a difference of one grade, similar degrees of activity were recorded in the right and left lungs or in the right middle and lower lobes. In each patient the highest grading value was used to indicate the true state of disease activity.

Complications of Transbronchial Biopsy

The transbronchial procedure was complicated by 3 unilateral pneumothoraces, an incidence of 15%. The pneumothoraces were diagnosed by fluoroscopy during the procedure in 2 of the 3 patients. The initial radiograph taken 2 hours after the procedure was normal in 1 patient and the pneumothorax occurred 4 hours later. All the pneumothoraces were drained. A substantial haemorrhage (>50 ml) was induced in 1 patient. This ceased spontaneously and the blood was effectively removed by suctioning under direct vision — an advantage of performing transbronchial biopsy through a rigid bronchoscope.

Total and Differential Alveolar Cell Counts

Total alveolar cell counts were determined in both the right middle lobe and the lingula in 4 patients with diffuse interstitial sarcoidosis and in 1 with IDUE. Based on the total cell count of the right middle lobe, the following percentage differences were recorded for the left lung in the 5 individuals: -4%, -3%, +3%, +16% and +31%. Macrophages, lymphocytes, neutrophils and

TABLE II. TOTAL AND DIFFERENTIAL ALVEOLAR CELL COUNTS (MEANS AND RANGES IN BRACKETS)

Diagnosis	Total count/ml	Macrophages	Differential cell count		
			Lymphocytes	Neutrophils	Eosinophils
Normal non-smokers (5)	50 000 (31 000 - 80 000)	95% (89% - 98%)	4% (1% - 9%)	1% (1% - 2%)	0%
Normal smokers (5)	124 000 (48 000 - 197 000)	91% (84% - 95%)	6% (4% - 8%)	3% (1% - 9%)	0% (0% - 2%)
Sarcoidosis (10)	290 200 (19 000 - 950 000)	70% (46% - 88%)	24% (8% - 41%)	3% (0% - 6%)	3% (0 - 29%)
IDUE					
Hypercellular type (3)	284 000 (121 000 - 524 000)	52% (38% - 79%)	33% (20% - 60%)	14% (1% - 40%)	0%
Hypocellular type (3)	27 700 (20 000 - 40 000)	94% (87% - 98%)	4% (1% - 8%)	2% (1% - 8%)	0%
Pigeon-fancier's disease (2)	1 012 500 (323 000 - 1 702 000)	32% (23% - 36%)	58% (53% - 62%)	8% (6% - 9%)	3% (2% - 4%)
Chronic eosinophilic pneumonia (2)	91 500 (35 000 - 148 000)	45% (25% - 65%)	26% (25% - 26%)	21% (3% - 28%)	9% (6% - 12%)

eosinophils expressed as mean percentages of the total number of cells in all four histopathological categories of patients are summarized in Table II.

The mean number of cells per millilitre of lavage solution was 50 000 (31 000 - 80 000) for non-smokers and 124 000 (48 000 - 197 000) for normal individuals who smoked. Alveolar lavage specimens of normal non-smokers and smokers contained 95% and 91% macrophages, 4% and 6% lymphocytes and 1% and 3% neutrophils respectively. Only 1 individual (a smoker) in the whole group of 10 normal smokers and non-smokers had 2% eosinophils. In the group with sarcoidosis 70% of the total number of alveolar cells were macrophages and 24% were lymphocytes. Eosinophils (29% of the total number) were found in only 1 patient. The total number of cells in this group was 290 200/ml lavage effluent. Only 1 patient with sarcoidosis had a total count below 90 000/ml (19 000). In 3 of the 6 patients with IDUE who had high total cell counts the lesion was termed 'hypercellular' and in the 3 with low values it was termed 'hypocellular'. Patients with hypercellular IDUE had a mean total count of 284 000/ml (121 000 - 524 000) while a mean total count of 27 700/ml (20 000 - 40 000) was recorded in the hypocellular IDUE group. Macrophages and lymphocytes accounted for 52% and 33% respectively of the total number of cells in the hypercellular IDUE group. A high neutrophil count of 40% was present in 1 patient in this group. The differential cell count of the subgroup with hypocellular IDUE was characterized by the presence of the 94% macrophages and 4% lymphocytes. The total and differential alveolar cell counts of patients with hypocellular IDUE were therefore very similar to those of the normal controls. The disease process in patients with hypocellular IDUE was considered inactive and this view was supported by the histopathological results. The differential count in the 2 patients with pigeon-fancier's disease was characterized by a high lymphocyte count of 58% and a low macrophage value of 32%. An 8% polymorph count was recorded in this group. The mean total cell count of

1 012 500/ml (range 323 000 - 1 702 000) was the highest of all the subgroups. Macrophage values of 25% and 65% were found in 2 patients with chronic eosinophilic pneumonia. A mean lymphocyte value of 26% and an eosinophil count of 9% were recorded in this subgroup, and 1 of these patients had a polymorph count of 28%. The total cell counts of these 2 patients were 35 000 and 148 000/ml. Because of the small numbers of patients in the respective subgroups, only the two main groups of normal and diseased patients were evaluated statistically.

No evidence of active interstitial disease was present in the 3 patients with hypocellular IDUE and they were excluded from the statistical analysis of the lymphocyte-macrophage (L-M) ratios and total alveolar cell counts. The geometric mean L-M ratio of 0,03 in normal controls (smokers and non-smokers) differed significantly ($P < 0,001$) from the mean L-M ratio of 0,3 in 17 patients with active interstitial disease. The mean total cell count in the 10 normal controls was 69 660/ml, significantly lower than the 205 600/ml of the 17 patients with active interstitial disease ($P < 0,01$).

Relationship between Alveolar Cell Counts and Histopathological Grading

A mean L-M ratio of 0,075 was recorded in 6 patients whose transbronchial biopsy specimens showed no activity (grade 0) or were graded 1-2+. In the 14 patients in whom histopathological examination showed high degrees of activity a geometric mean L-M ratio of 0,579 was recorded. A statistical difference ($P < 0,001$) was found between the geometric mean L-M ratios of patients with low and high degrees of disease activity. This correlation of L-M ratios with histopathological degrees of disease activity was based on entirely independent observations.

Assessment of Disease Activity by Alveolar Lavage and Radiography

Radiographical activity was related to the L-M ratio and histopathological assessment of activity in 17 patients

TABLE III. DISEASE ACTIVITY — CYTOLOGICAL, HISTOPATHOLOGICAL AND RADIOLOGICAL ASSESSMENTS

Diagnosis	Degree of activity		
	L-M ratio (normal 0,03)	Histopathological (0 - 4)	Radiographic (0 - 7)
Sarcoidosis			
1	0,46	4	4
2	0,09	3	7
3	0,52	3	7
4	0,26	3	6
5*	0,24	1	3
6	0,76	3	7
7	0,18	4	6
8	0,5	4	5
9	0,61	3	6
IDUE			
Hypercellular			
10*	1,58	3	2
11	0,50	3	6
Hypocellular			
12	0,01	2	3
13	0,02	1	3
Pigeon fancier's disease			
14*	2,21	4	0
15	1,47	3	7
Chronic eosinophilic pneumonia			
16	0,4	3	6
17	1,00	3	5

* Indicates subjects in whom radiological and histopathological assessments of disease activity and L-M ratios were not in conformity.

(Table III). Nine of these patients had sarcoidosis, 4 IDUE, 2 pigeon-fancier's disease and 2 chronic eosinophilic pneumonia. A radiological assessment of 0-3 was classified as a low and one of 4-7 as a high degree of disease activity. In 12 of the 17 patients, high radiological grades were associated with high L-M ratios and histopathological assessment. In 2 patients all three parameters were graded 'low' (No. 12 and 13). In 2 patients the radiological assessment of activity was low, while high L-M ratios and histopathological grading were recorded (No. 10 and 14). Low grades of activity on radiological and histopathological grading were associated with a high L-M ratio in 1 subject (No. 5). Conformity was therefore achieved by all three assessment techniques in 14 out of 17 patients.

DISCUSSION

Evaluation of the degree of disease activity has become an essential prerequisite for rational therapy and follow-up of patients with interstitial lung disease. Gallium-67-citrate scintigraphy is a non-invasive technique that was employed for this purpose by Crystal *et al.*⁸ It has the disadvantage of radiation exposure when employed repeatedly for follow-up purposes. Reports on the alveolar cytology of patients with interstitial disease indicate that it relates to the degree of cellularity of the disease process.⁶⁻⁸ A quantitative correlation needs to be established, however, between results of this investigation and histopathological or radiological parameters of disease activity.

Nonspecific changes have been reported when differential alveolar cytology was used to establish the aetiology of interstitial lung disease. Weinberger *et al.*⁷ found high lymphocyte counts in patients with sarcoidosis and hypersensitivity pneumonitis. High neutrophil counts have been reported by Crystal *et al.*⁸ on the differential alveolar cytology of patients with IDUE. Studies in which differential alveolar cytology has been related to the histopathological changes of interstitial disease have been based on open lung biopsy specimens.⁶⁻⁸

By comparison transbronchial biopsy is a relatively non-invasive procedure. As technique for determining the aetiology of interstitial lung disease, it has provided reliable results. Tissue yields of 79-93% and aetiological diagnoses of 48-85% have been reported.^{4,5,9-11} A histopathological diagnosis was made in 60% of the patients with interstitial disease in this study and a tissue yield of 95% was achieved. Positive clinical, radiological and cytological evidence was found in these patients. In 6 patients (30%) a diagnosis of IDUE was made. This figure for nonspecific interstitial pneumonitis and fibrosis compares well with the 27-48% reported in other studies in which transbronchial biopsy was utilized.^{12,13} The histopathological report of organizing pneumonia in 2 patients (10%) was not diagnostic. The radiological picture described by Gaensler and Carrington¹⁴ as 'the photographic negative of pulmonary oedema', as well as the swift response to corticosteroid therapy, supported the clinical diagnosis of chronic eosinophilic pneumonia.

Of the total number of alveolar cells eosinophils accounted for 6% and 12% in these 2 patients. These results illustrate the value of conducting alveolar lavage and transbronchial biopsy together during the initial assessment of patients with interstitial lung disease. Evaluation of alveolar lavage effluent by differential cell counting, cytological assessment for cancer and culture in immunocompromised hosts, can supplement biopsy in establishing the cause of a disease process.

The possible complications of performing multiple transbronchial biopsies have to be considered. The unilateral pneumothoraces in 3 patients (15%) and limited haemorrhage in 1 patient (5%) compare favourably with the incidence of 14% for pneumothorax and 1% for haemorrhage reported by Anderson *et al.*,²⁵ who conducted unilateral biopsy during rigid bronchoscopy in 525 subjects. In the present study, care was taken to exclude development of a pneumothorax after each biopsy, before proceeding to the next biopsy site. The fact that two of the three pneumothoraces reported in this series developed during the biopsy procedure stresses the importance of employing fluoroscopy. Routine follow-up radiography within 2-4 hours serves as an additional safety measure to diagnose the delayed appearance of this complication. To date, multiple bilateral transbronchial biopsies have been performed safely on 38 patients, with a 14% incidence of unilateral but no bilateral pneumothoraces. The potential influence of observer bias on the estimation of disease activity was controlled in 10 randomly selected patients. For this purpose disease activity was reassessed on biopsy specimens obtained from different lobes or separate lungs, without the observer knowing the clinical diagnosis or site of origin of individual specimens. Similar degrees of activity with differences of one grade only were found in specimens obtained from widely separated anatomical areas in 8 of 10 subjects (Table I). These results suggest that transbronchial biopsy can provide representative tissue samples and that consistency in the estimation of disease activity can be achieved.

An association was found between the histopathological assessment of activity and the L-M ratio in the patients with radiological and clinical evidence of interstitial disease. Patients whose lung specimens were graded as showing low degrees of activity (1-2+) had low L-M ratios whereas high grading on histopathological examination was associated with a high L-M ratio. Two patients from whom single biopsy specimens were obtained showed low degrees of disease activity on histopathology despite high L-M ratios. An explanation for this discrepancy could be that the lavage effluent in terms of cellularity reflected a larger area of diseased lung and could theoretically be more representative than the biopsy specimen. A combination of these two investigative procedures can therefore enhance the physician's ability to gauge the degree of disease activity. The L-M ratio and, to a lesser extent, the total alveolar cell count appear to be representative parameters of disease activity regardless of the aetiology of the interstitial lung disease. In comparison to transbronchial biopsy, alveolar lavage carries no morbidity and it may therefore be useful for repeated assessment of

disease activity in patients on high-dose corticosteroid treatment.

A standardized technique for conducting alveolar lavage and for processing the retrieved cells does not exist at present. Varying volumes of saline (100-300 ml) and different instruments, e.g. fibre-optic bronchoscopes and catheters, have been employed for this purpose.^{8,16-19} By placement of a catheter in a subsegmental bronchus, contamination with cells from the trachea and mainstem bronchi was avoided, a relatively important consideration for excluding inflammatory reactions in larger airways from influencing the total and differential alveolar cell counts. Small volumes of saline were instilled and removed and this method could provide more representative cell samples from the distal lung than when a single large volume of fluid is used. Bronchoscopy is not essential for conducting follow-up alveolar lavage procedures in patients with interstitial disease. This has been performed on an outpatient basis in 6 of the patients in this study by selective segmental catheterization under fluoroscopy with a remote control selector-catheter (Medi-Tech, Belmont, Mass., USA) or with a Machida catheter. Alveolar lavage in both the right and the left lungs of 5 individuals produced comparable numbers of cells. These results suggest that representative cell samples can be obtained by lavage from any lung segment in patients with interstitial lung disease. A mean volume of 44 ml (range 17-85 ml) of alveolar effluent was obtained from the control and diseased patients. This variable factor has been documented in similar studies by Daniele *et al.*¹⁶ and by Reynolds and Newball.¹⁷ For determination of the alveolar cell count it can be circumvented by expressing the number of alveolar cells per millilitre of retrieved solution. No statistical correlation was found in this study between the total retrieved volume and the alveolar cell count per millilitre of lavage effluent. Within the control group the cigarette smokers had a higher mean total alveolar cell count per millilitre of lavage solution than the non-smokers. This is a well-known phenomenon.^{17,20,21} The L-M ratios of smokers and non-smokers were, however, similar. In the group with interstitial disease, no statistical difference was recorded between the mean total cell counts of the 7 smokers and the 13 non-smokers ($P>0.05$). The abnormal total and differential cell patterns of patients with interstitial disease therefore appears to be a function of the disease process and not of cigarette consumption. In 14 of 17 patients the radiological estimation of disease activity was in keeping with the histopathological and alveolar cell results. In three patients the radiologist's estimation of degree of disease activity was low, while high L-M ratios (3 subjects) and high histopathologically determined degrees of activity (2 patients) were reported. This phenomenon of a normal or near-normal chest radiograph in patients who have very active, cellular interstitial disease has also been reported by Epler *et al.*²² These data indicate that an experienced radiologist can in most cases roughly estimate the degree of disease activity in interstitial lung disease. Active disease could, however, be grossly underestimated if one relied solely on a radiological opinion.

Transbronchial biopsy, alveolar lavage and radiography,

when employed singly in the initial assessment of the disease, will lead to inevitable errors. However, in combination, these three techniques supplement one another and provide a safe and, if necessary, repeatable means of planning rational therapy and determining prognosis.

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Intra-uterine Growth in Infants of Diabetic Mothers

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SUMMARY

The birth weight, length, head circumference and body proportions of infants born to women with well-controlled diabetes were compared with those of infants born to poorly controlled diabetics. The latter infants were significantly heavier, with a greater weight/length ratio and a smaller head circumference/weight ratio, while their length, and head circumference/length ratio were appropriate for age. The size and body proportions of infants born to well-controlled diabetics were normal. Hairiness of the pinna was observed in infants born to both well- and poorly controlled diabetics, and may prove to be a useful clinical sign in identifying the infant of a diabetic mother.

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If diabetes is strictly controlled during pregnancy normal fetal growth can be achieved, resulting in appropriate birth weight, length and head circumference for gestational age.¹ Infants born to women whose diabetes is poorly controlled, however, are frequently overweight.² Whether their length is abnormal remains controversial,³ while their head circumference has not been documented.

The purpose of this study, therefore, was to compare the weight, length, head circumference and body proportions in infants born to women with well-controlled and those with poorly controlled diabetes.

METHODS

Eighty-one singleton infants born to women suffering from diabetes mellitus were studied prospectively. Still-born infants and those with major congenital abnormalities were excluded. In all the mothers two or more of the following values were shown to be abnormal during a 50 g oral glucose tolerance test: (a) fasting blood glucose levels of > 5.5 mmol/l; (b) a peak level of > 10 mmol/l; and (c) a 2-hour level of > 6.7 mmol/l. Blood glucose was estimated on capillary samples using a Beckman glucose analyser.